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DOI: https://doi.org/10.1093/brain/aws217

doi:10.1093/brain/aws217 Brain 2012: 135; 1–1 | e220

BRAIN
A JOURNAL OF NEUROLOGY

LETTER TO THE EDITOR

When is the time right for a Phase III clinical study in spinal cord injury ($P = 0.05$)?

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Sir, it was a great pleasure to read the findings from a completed Phase II minocycline study in acute spinal cord injury recently published in *Brain* (Casha *et al*., 2012). In light of the fact that there are currently no available neuroprotective treatment options for individuals with acute spinal cord injury, it was encouraging to find that minocycline can be feasibly administered in a short timeframe after injury (12 h) and is safe at therapeutic concentrations. However, Casha *et al*.'s (2012) conclusion to enter a pivotal Phase III trial warrants further discussion.

After stratifying for injury heterogeneity (i.e. complete and incomplete injuries, cervical and thoracic levels) and different treatment groups (i.e. high and low concentrations), Phase II clinical trials in spinal cord injury are generally underpowered statistically to measure significant therapeutic effects. To account for the variability introduced by small sample sizes, historical data (i.e. based on findings of well-controlled databases comprising neurological outcomes acquired during the transition from acute to chronic spinal cord injury) could be of value to appreciate the meaning of changes in early phases of clinical study. In individuals with severe incomplete cervical spinal cord injury [Abbreviated Injury Scale (AIS0 C)], recent estimates of motor recovery range on average from 43 (Curt *et al*., 2008) to 46 points (Marino *et al*., 2011). Attributable to a ceiling effect, individuals with less severe incomplete spinal cord injury (AIS D) actually recover fewer motor points (~20) (Curt *et al*., 2008; Marino *et al*., 2011). Thus, while a 48–50 motor point change in the motor-incomplete cervical spinal cord injury group treated with minocycline (80% of whom were AIS C) is slightly higher than historical control values, it is well within the expected high degree of variability introduced by the low number of subjects ($n = 5$). Furthermore, the difference between minocycline and placebo may have been exaggerated by the fact that individuals receiving placebo recovered so few motor points spontaneously—a finding potentially related to a high proportion of AIS D subjects in this group.

We remain optimistic that minocycline may be a viable option for neuroprotection in acute spinal cord injury. However, given the detrimental impact of another failed Phase III study in the field of spinal cord injury, and the available evidence, it may be premature to consider minocycline ready for a multicentre, pivotal trial. Rather, the next step should be to optimize patient stratification to reflect where the benefit of minocycline may be most readily detected.

Funding

John Kramer was funded by the International Foundation for Research in Paraplegia - Zurich.

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Advance Access publication September 3, 2012